

## CSM/SSRIsWG/03/1<sup>st</sup> MEETING

### COMMITTEE ON SAFETY OF MEDICINES

#### EXPERT GROUP ON SAFETY OF SSRIs

#### MINUTES OF THE MEETING HELD ON FRIDAY 23 MAY 2003 AT 1PM IN CONFERENCE ROOM (2) AT MARKET TOWERS

##### Members present:

Professor G Duff (Acting Chairman)  
Professor D Ashby  
Mr R Brook  
Dr J Chick  
Professor C Drummond  
Professor K Ebmeier  
Dr R Mukaetova-Ladinska  
Mr E O'Tierney  
Dr R J Taylor

##### Apologies

Dr D Gunnell  
Professor IVD Weller

##### Professional staff of MHRA

Dr C Hawkins	MHRA/PL
Mr J Mean	MHRA/PL
Dr J Raine	Director of Post Licensing
Ms S Wark	MHRA/PL
Dr J Williams	MHRA/PL
Dr L Wise	MHRA/PL

##### Observers

Dr J Moseley	MHRA/PL
Dr C Parikh	MHRA/PL
Dr P Raptopoulos	MHRA/PL

##### Department of Health

Dr A Higgitt – Mental Health Services  
Miss A Langley – Press Office

### 1.0 INTRODUCTION

- 1.1 Professor Duff (the acting Chair) welcomed members of the Group and thanked them all for coming to the meeting.
- 1.2 Professor Duff explained that he would be acting as Chair for this initial meeting only and that future meetings would be Chaired by the Professor Ian Weller, who had a prior commitment on this date.
- 1.3 The Chairman explained that the purpose of the meeting was primarily to provide the Group with background to the Medicines and Healthcare products Regulatory Agency (MHRA) and Committee on safety of Medicines' (CSM) previous consideration of the safety of the Selective Serotonin Reuptake Inhibitors (SSRIs) and all relevant information that had previously been considered by the CSM. The papers provided to the Group on the issues of particular concern, namely withdrawal reactions and suicidal behaviour, would provide the background for consideration of these issues during future meetings.

- 1.4 The Chairman informed members that the issues considered by the Expert Working Group are confidential and that members should not speak directly to the press but should refer any enquiries to the Chairman, MCA or Press Office. At scientific meetings, they should take care not to give the impression that they speak on behalf of the Group.
- 1.5 Apologies were received from Professor Ian Weller and Dr David Gunnell.
- 1.6 The question was raised as to whether a code of confidentiality that the members of the Group have been asked to agree to would prevent them from discussing general matters regarding the SSRIs. The Chairman explained the confidentiality specifically relates to issues or papers considered by the Group and not to general issues relating to SSRIs. It was agreed that if members were unclear on any matter they should contact the secretariat for clarification.

## **2.0 DECLARATION OF INTERESTS**

- 2.1 Mr Richard Brook declared a lapsed non-personal interest in Astra Zeneca but this did not debar him from taking part in the proceedings. Professor Ebmeier declared a personal non-specific interest in Lundbeck. Professor Ebemier informed the Group that he received a payment from Lundbeck in return for attending a focus group on Alzheimer's disease. The amounts were relatively small and the payment did not relate to Lundbeck's SSRI product. The payments were made less than a year ago, but are not on-going. In light of this information the legal advice was that this was not therefore a current personal interest. Professor Ebmeier would continue to declare this at meetings of the Group. In addition this information would need to appear on the website. The Group noted that both the acting Chair and Dr Mukaetova-Ladinska would supply information to the Group about their non-personal interests.

## **3.0 REMIT OF EXPERT WORKING GROUP**

- 3.1 The Group agreed the following remit:

to consider the currently available evidence with regard to behavioural disorders, particularly suicidal behaviour, suicide attempt and suicide, and a possible causal association with SSRIs;

to consider the currently available evidence on withdrawal reactions and possible dependence associated with SSRIs and any implications for the risk: benefit balance;

to consider the adequacy of the current product information for SSRIs and to make proposals to strengthen this if necessary;

to consider the need for wider communication on the safety of SSRIs;

and to advise the Committee on Safety of Medicines.

- 3.2 The Group agreed that the term behavioural disorders should encompass aggression, violence and homicide.

#### **4. PROCEDURAL ITEMS**

- 4.1 The Group was keen to ensure that they had all relevant data relating to the safety of SSRIs. The secretariat agreed to perform a full literature search to ensure that the most up to date literature in this area had been provided to the Expert Group
- 4.2 Members of the Group noted a lack of precision or clarity over some of psychiatric and regulatory terms which had been used in the papers submitted to the Expert Group. It was agreed that the secretariat would prepare a glossary of all relevant psychiatric and regulatory terms for members of the Group.
- 4.3 The Group commented that it would be helpful to have contact details of the relevant agency personnel and the secretariat agreed to provide this.
- 4.4 At the request of the Group the secretariat agreed to provide members with an index of all the papers presented to the Expert Group.

#### **5.0 SSRIS – UPDATE ON REGULATORY ACTIVITY**

- 5.1 An overview of the history of the MHRA/CSM review of the safety of SSRIs was presented to the Group, with particular focus on the two main areas of concern: withdrawal reactions and suicidal behaviour (attached as an annex to these minutes).
- 5.2 It was agreed that a copy of this presentation should be circulated to the Group for information.
- 5.3 The Group was informed that the applications for the renewal of the Marketing Authorisation for Seroxat Tablets had been submitted to the MHRA and these applications would be considered by the Group during the forthcoming meetings.

#### **6.0 SSRIS – WITHDRAWAL REACTIONS AND DEPENDENCE**

##### **6.1 Update on evidence**

- 6.1.1 The Group was informed of the action that has been taken since 1993 with regard to withdrawal reactions and possible dependence in association with all SSRIs including the most recent consideration of the CSM in 1998/99. From a detailed review of all available data, the CSM has concluded that:

- all SSRIs can cause withdrawal reactions;
- the frequency of withdrawal reactions differs between SSRIs;
- no strong evidence had been identified to suggest that SSRIs cause other features of dependence.

6.1.2 As a result of this review product information for all SSRIs was updated.

6.1.3 This issue was also reviewed at a European level at the Committee on Proprietary Medicinal Products (CPMP). The CPMP reached similar conclusions and published its position on this issue in a paper, which is available on the European Medicines Evaluation Agency (EMA) website.

6.1.4 The Group noted the current position on withdrawal reactions with SSRIs and commented on the need to consider the definition of dependence, whether based upon that definition the available data on withdrawal reactions are indicative of dependency.

## **6.2 Frequency of withdrawal reactions with paroxetine**

6.2.1 The Group was informed that at the request of the MHRA, the Marketing Authorisation (MA) holder for Seroxat (paroxetine), GlaxoSmithKline, had submitted data on the frequency of withdrawal reactions from recent placebo-controlled clinical trials where paroxetine has been used in the treatment of generalised anxiety disorder and posttraumatic stress disorder. The percentage of patients who reported adverse events potentially related to withdrawal of treatment was 25.7% in the paroxetine group and 15.4% in the placebo group. The MA holder considered that when corrected for placebo the percentage of patients who experience withdrawal reactions when stopping paroxetine is 10%.

6.2.2 The Group was asked to consider whether, based on the data submitted, by the MA holder the figure of 10% was a valid estimate of the incidence of withdrawal reactions that is attributable to stopping treatment with paroxetine.

6.2.3 The Group advised that it would aid both prescribers and patients understanding if the SPC and PIL more clearly reflected the fact that although 25% of patients may experience withdrawal reactions on stopping treatment with paroxetine, only 10% of patients will experience a withdrawal reactions on stopping treatment that is attributable to paroxetine.

6.2.4 The Group was asked to provide written comments on this paper by close of business on 30 May 2003.

## **6.3 Draft Report of WHO Expert Committee on Drug Dependence**

6.3.1 The Group noted this information.

## **7.0 SSRIS AND SUICIDAL BEHAVIOUR**

- 7.1 The Group was informed that the CSM has conducted reviews of suicidal behaviour and its possible association with SSRIs in 1991, June 2000 and most recently in December 2001. The CSM have concluded that the current evidence is insufficient to confirm a causal association between SSRIs and suicidal behaviour. This uncertainty is due to the nature and natural history of depressive illness. CSM had advised that this issue should continue to be kept under close review.
- 7.2 The Group noted the papers provided and the current CSM position.

## **8.0 PATIENT REPORTS**

### **8.1 'Paroxetine, Panorama and user reporting of ADRs: Consumer intelligence matters in clinical practice and post-marketing surveillance'**

- 8.1.1 The Group noted this paper, which had recently been published in the International Journal of Risk & Safety in Medicine.

### **8.2 Overview of the *Panorama*/Mind Yellow Cards and proposal for full evaluation**

- 8.2.1 The Group was informed that in response to a Panorama programme entitled 'Secrets of Seroxat' which was broadcast in October 2002, Panorama received 1,374 emails. Following this large public response Panorama in association with Mind created a Panorama/ Mind Yellow Card or questionnaire to obtain specific about the patients' experiences with Seroxat.
- 8.2.2 A total of 239 Panorama/Mind Yellow Cards were collated and evaluated for a follow-up programme entitled 'Panorama:Seroxat:Emails from the edge'. This programme was broadcast on 11 May 2003, following which these Panorama/Mind reports were submitted to the MHRA for evaluation. Of the quoted 239 reports 223 were received by the MHRA. The MHRA has contacted Panorama to clarify the discrepancy in numbers.
- 8.2.3 The Group was informed that in order that these reports and the information they contain are processed as rapidly and effectively as possible, key information from these reports would be entered onto an Excel spreadsheet. The data from these reports would then be analysed according to the following groupings:
- 8.2.4 Various symptoms and suspected adverse drug reactions associated with paroxetine; Symptoms associated with stopping treatment and consequent difficulty in stopping; Suicide, suicidal ideation and self-harm.

- 8.2.5 The Group commented that further emails had been received following the follow-up programme in May 2003 and that MHRA should contact Panorama to obtain this additional information.
- 8.2.6 The Group was asked to provide written comments on the proposed for full evaluation of these reports by close of business on the 30 May.

## **9.0 DRAFT GPRD STUDY PROTOCOL**

- 9.1 The Group was informed of a study to be conducted by the MHRA using the General Practice Research Database (GPRD). The first aim of this study is to investigate and to compare odds of suicide for the SSRIs with the odds for the most frequently prescribed tricyclic antidepressants. An additional analysis will compare the odds of suicide for the individual SSRIs compared to the odds of suicide for fluoxetine. A second aim is to investigate and compare the odds of suicide for patients prescribed an SSRI with a record of depression in their notes with patients prescribed an SSRI with no record of depression in their notes. This analysis will investigate whether any increased relative risk is associated with a drug effect or a disease effect.
- 9.2 The Group commented that it was important to be aware of the differing definitions of suicide employed by the Procurator Fiscal in Scotland compared with coroner in England and Wales. The Group also considered that the risk of attempted suicide should also be investigated.
- 9.3 The Group was asked to provide written comments on this draft protocol by close of business on 30 May.

## **10.0 CURRENT AND PROPOSED SEROXAT PATIENT INFORMATION LEAFLET**

- 10.1 The Group was informed that the MA holder for Seroxat had been asked to update the Seroxat Patient information leaflets to improve readability, to provide more information on possible withdrawal reactions including information on the frequency and severity of these reactions and to improve clarity of possible side effects that may occur whilst on treatment.
- 10.2 The Group was asked to provide written comments on the proposed amendments by close of business on the 30 May.

## **11.0 SEROXAT - PAEDIATRIC SAFETY AND EFFICACY DATA**

- 11.1 The Committee was informed that on 21 May 2003, GlaxoSmithKline submitted to MHRA a briefing document summarising clinical trial data on Seroxat (paroxetine)

in the treatment of paediatric obsessive compulsive disorder, social anxiety disorder and major depressive disorder (MDD), in preparation for discussion of forthcoming variations to extend the indications to the paediatric age group. The results from the trials in adolescents and children in the submission (particularly those in MDD) raised a safety signal.

- 11.2 The Group was informed that the MHRA had requested that the MAH submit all relevant data immediately and that these data would be urgently considered by the CSM at its meeting on 29 May. The Group was asked for written comments on the data by close of business 29 May.

## **12.0 ANY OTHER BUSINESS**

- 12.1 The Chairman informed the Group of the following proposed dates for future meetings:

18 June 2003  
22 July 2003  
16 September

- 12.2 The Group was asked to confirm the availability on these dates with the secretariat as soon as possible.

**Post Licensing Division  
MHRA**